

What is claimed is:

1. A process for preparing crystalline nateglinide Form B comprising heating a crystalline form of nateglinide selected from the group consisting of Form A, C, D, F, G, J, Q, T, α , β , δ , ε , θ and Ω to obtain nateglinide Form B.
- 5 2. The process of claim 1, wherein the nateglinide is Form α .
3. The process of claim 1, wherein the nateglinide is Form δ .
4. A process for preparing nateglinide Form B comprising the steps of:
 - a) preparing a suspension of nateglinide in a C₅ to a C₁₂ hydrocarbon;
 - b) adding a solvent selected from the group consisting of an alcohol, an ester, a
- 10 ketone or mixtures thereof to the suspension to obtain a solution;
- c) crystallizing nateglinide Form B from the solution in the absence of stirring; and
- c) recovering the nateglinide Form B.
5. The process of claim 4, wherein the hydrocarbon is selected from the group consisting of heptane, hexane, toluene and xylene.
- 15 6. The process of claim 4, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-propanol, acetone and ethyl acetate.
7. The process of claim 6, wherein the solvent is ethyl acetate.
8. The process of claim 4, wherein crystallizing is carried out by seeding and cooling.
9. The process of claim 4, wherein Form B crystallizes at a crystallization temperature of
- 20 higher than about 15°C.
10. The process of claim 4, wherein the solvent/hydrocarbon combination is ethyl acetate/heptane or hexane.
11. A process for preparing crystalline nateglinide Form B comprising the steps of:
 - a) preparing a solution of nateglinide in a mixture of ethyl acetate and a C₅ to a C₁₂
- 25 hydrocarbon;
- b) crystallizing nateglinide Form B from the solution; and
- c) recovering the nateglinide Form B.
12. The process of claim 11, wherein the crystallizing step is carried out in the absence of stirring.
- 30 13. The process of claim 11, wherein preparing a solution involves preparation of a first solution of nateglinide in ethyl acetate, followed by combining the first solution with the hydrocarbon.

14. The process of claim 11, wherein crystallization is carried out at a temperature of higher than about 15°C.

15. A process for preparing nateglinide Form B comprising the step of storing nateglinide Form A at a suitable temperature for a sufficient amount of time to obtain nateglinide Form B.

16. A process for preparing nateglinide Form B comprising the steps of:

- preparing a solution of nateglinide in a solvent selected from the group consisting of an ester, ketone, amine, amide, alcohol, nitrile; and
- removing the solvent to obtain nateglinide Form B.

17. The process of claim 16, wherein the solvent is selected from the group consisting of acetonitrile, acetone, ethyl acetate and iso-propyl alcohol.

18. The process of claim 16, wherein removing involves evaporation of the solvent.

19. The process of claim 18, wherein the solvent is evaporated at a temperature of from about 40°C to about 70°C.

20. A process for preparing nateglinide Form B comprising the step of triturating nateglinide Form δ in ethyl acetate at a suitable temperature for a sufficient amount of time to obtain nateglinide Form B.

21. The process of claim 20, wherein the temperature is at least about 40°C.

22. A process for preparing nateglinide Form B comprising the steps of:

23. a) preparing a solution of nateglinide in ethyl acetate;

24. b) concentrating the solution to precipitate nateglinide Form B; and

25. c) recovering the nateglinide Form B.

26. A process for preparing nateglinide Form B comprising the steps of:

- preparing a solution of nateglinide in a mixture of water and isopropanol;
- crystallizing nateglinide Form B from the solution; and
- recovering the nateglinide Form B.

27. A process for preparing nateglinide Form B comprising the steps of:

- preparing a solution of nateglinide in a mixture of isopropanol and water;
- seeding the solution with nateglinide Form B at a temperature of from about 25°C
- to about 35°C;
- stirring the solution;

- d) cooling the solution to a temperature of about minus 5°C to about 5°C to obtain a slurry;
- e) stirring the slurry;
- f) recovering a solid from the slurry; and
- 5 g) heating the solid to obtain nateglinide Form B.

25. A crystalline form of nateglinide (Form L) characterized by data selected from the group consisting of: an XRPD pattern with peaks at 17.6, 17.9 and 19.6 ± 0.2 degrees 2θ, a DSC thermogram with endotherms at about 131 and 138°C and an FTIR spectrum with 10 peaks at about 1741, 1726, 1621, 1600, 1538, 1211, 1191 cm^{-1} .

26. The crystalline form of claim 25, wherein the crystalline form is characterized by an XRPD pattern with peaks at 17.6, 17.9 and 19.6 ± 0.2 degrees 2θ.

27. The crystalline form of claim 26, wherein the crystalline form has an XRPD pattern as substantially depicted in Figure 10.

15 28. The crystalline form of claim 25, wherein the crystalline form is stable when heated at a temperature of about 100°C for at least about 8 hours.

29. A process for preparing nateglinide of claim 25 comprising the step of heating a nateglinide selected from the group consisting of Form D, M and N for a sufficient amount of time to obtain the nateglinide of claim 25.

20 30. A process for preparing nateglinide of claim 25 comprising the step of storing nateglinide Form I at a suitable temperature for a sufficient time to obtain the nateglinide of claim 25.

31. A crystalline form of nateglinide (Form P) characterized by data selected from the group consisting of: an XRPD pattern with peaks at 4.0, 4.6, 13.4, 13.9 and 19.1 ± 0.2 degrees 2θ;

25 an FTIR spectrum with peaks at about 3309, 1748, 1589 cm^{-1} ; and a DSC thermogram with endotherms at about 106 and 128°C and an exotherm at about 113°C.

32. The crystalline form of claim 31, wherein the crystalline form is characterized by an XRPD pattern with peaks at 4.0, 4.6, 13.4, 13.9 and 19.1 ± 0.2 degrees 2θ.

30 33. The crystalline form of claim 32, wherein the crystalline form has an XRPD pattern as substantially depicted in Figure 14.

34. A process for preparing the crystalline nateglinide of claim 31 comprising the steps of:

a) triturating nateglinide in a solvent selected from the group consisting of acetone, nitromethane and acetonitrile to obtain the crystalline form of claim 31, with the proviso that the nateglinide triturated in nitromethane is not Form H; and

b) recovering the crystalline form of nateglinide.

5 35. The process of claim 34, wherein the nateglinide triturated is Form H and the solvent is acetonitrile.

36. The process of claim 34, wherein the nateglinide triturated is Form U and the solvent is acetone or nitromethane.

37. A process for preparing nateglinide of claim 31 comprising the step of heating 10 nateglinide Form epsilon for a sufficient amount of time at a suitable temperature.

38. A process for preparing nateglinide Form S comprising the step of heating a nateglinide selected from the group consisting of Form K, I and α for a sufficient amount to obtain nateglinide Form S.

39. The process of claim 38, wherein the nateglinide heated is Form α .

15 40. A process for preparing nateglinide Form S comprising the steps of:

- a) preparing a solution of nateglinide in n-butanol or di-methyl formamide;
- b) crystallizing nateglinide from the solution;
- c) recovering the nateglinide; and
- d) heating the nateglinide to obtain Form S.

20 41. A process for preparing nateglinide Form U comprising the steps of:

- a) preparing a solution of nateglinide in a mixture of a solvent selected from the group consisting of an ester, ketone, alcohol and mixtures thereof, and an anti-solvent;
- b) crystallizing nateglinide Form U from the solution; and
- c) recovering the nateglinide Form U.

25 42. The process of claim 41, wherein the anti-solvent is a C₅ to a C₁₂ hydrocarbon.

43. The process of claim 42, wherein the anti-solvent is heptane.

44. The process of claim 41, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, n-butanol, n-propanol, acetone and ethyl acetate.

45. The process of claim 44, wherein the solvent is ethyl acetate.

30 46. The process of claim 45, wherein ethyl acetate to anti-solvent ratio is from about 2:1 to about 1:1 (vol/vol).

47. The process of claim 46, wherein the anti-solvent is from about 20°C to about 40°C colder than the ethyl acetate.

48. The process of claim 47, wherein the anti-solvent has a temperature of from about 0°C to about 10°C and the ethyl acetate a temperature of from about 30°C to about 40°C.

49. The process of claim 41, wherein Form U is prepared by preparing a solution having a temperature of at least about 25°C, followed by cooling to a temperature of from about 5 0°C to about 10°C to crystallize Form U, and recovery of Form U before its transition to another form.

50. A process for preparing nateglinide Form U comprising the steps of:

- adding a solution of nateglinide in ethyl acetate to a container holding heptane to spontaneously precipitate nateglinide Form U, wherein the heptane is colder than the 10 solution; and
- recovering the nateglinide Form U.

51. A process for preparing nateglinide Form U comprising the step of triturating nateglinide Form δ in ethyl acetate at a suitable temperature for a sufficient amount of time to obtain nateglinide Form U.

15 52. The process of claim 51, wherein the temperature is from about 20°C to about 30°C.

53. A process for preparing nateglinide Form U comprising the steps of:

- preparing a solution of nateglinide in ethyl acetate or acetone;
- seeding the solution with a crystalline form of nateglinide to crystallize nateglinide Form U; and
- recovering the nateglinide Form U.

20 54. The process of claim 53, wherein the solution is seeded with Form B.

55. A crystalline form of nateglinide (Form α) characterized by data selected from the group consisting of: an XRPD pattern with peaks at 4.8, 5.1, 19.0, 19.4, 27.2, 28.9 and 31.2 ±0.2 degrees 2θ; a DSC thermogram with an endotherm at about 129°C; and an FTIR 25 spectrum with peaks at about 3283, 1711, 1646, 1420, 1238 cm⁻¹.

56. The crystalline form of nateglinide of claim 55, wherein the crystalline form is characterized by an XRPD pattern with peaks at 4.8, 5.1, 19.0, 19.4, 27.2, 28.9 and 31.2 ±0.2 degrees 2θ.

57. The crystalline form of claim 56, wherein the crystalline form has an XRPD pattern as 30 substantially depicted in Figure 21.

58. The crystalline form of claim 55, wherein the crystalline form is stable when heated to a temperature of about 60°C for about 8 hours.

59. A process for preparing crystalline nateglinide of claim 55 comprising the steps of:

- triturating nateglinide in a solvent selected from the group consisting of methanol, n-butanol and ethanol to obtain the crystalline form of claim 55, with the proviso that the nateglinide triturated is not Form H; and

5 b) recovering the nateglinide Form α .

60. The process of claim 59, wherein the nateglinide triturated is Form U.

61. A process for preparing crystalline form of nateglinide of claim 55 comprising the steps of:

- preparing a solution of nateglinide in a solvent selected from the group consisting of n-propanol, n-butanol, isopropyl alcohol and acetonitrile;
- crystallizing the crystalline form from the solution; and
- recovering the crystalline form of claim 55.

62. A process for preparing crystalline nateglinide of claim 55 comprising the step of heating a form of nateglinide selected from the group consisting of Form K and Form C for a sufficient time to obtain the crystalline form.

63. A process for preparing a mixture of crystalline nateglinide Form α and Form H comprising the step of triturating a nateglinide in a solvent selected from the group consisting of methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone and dimethyl ethane.

20 64. The process of claim 63, wherein the nateglinide triturated is crystalline Form U.

65. A crystalline form of nateglinide nateglinide (Form δ) characterized by data selected from the group consisting of: an XRPD pattern with peaks at 5.6, 14.5, 18.2, 18.9 and 19.5 ± 0.2 degrees 2θ ; an FTIR spectrum with peaks at about 3306, 1729, 1704, 1275 cm^{-1} ; and a DSC thermogram with endotherms at about 100 and 130°C.

25 66. The crystalline nateglinide of claim 65, wherein the crystalline form is characterized by an XRPD pattern with peaks at 5.6, 14.5, 18.2, 18.9 and 19.5 ± 0.2 degrees 2θ .

67. The crystalline form of claim 66, wherein the crystalline form has an XRPD pattern as substantially depicted in Figure 24.

68. The crystalline form of claim 65, wherein the crystalline form is stable at a

30 temperature of about 40°C and a relative humidity of about 75% for at least about 3 months.

69. The crystalline form of claim 65, wherein the crystalline form is stable at a temperature of about 60°C after at least about 8 hours.

70. The crystalline form of claim 65, wherein the crystalline form is substantially free of nateglinide Form H.

5 71. A process for preparing the crystalline form of nateglinide of claim 65 comprising the step of stirring a nateglinide anhydrate for a sufficient time in an organic solvent, with the proviso that the organic solvent is a solvent other than only ethyl acetate.

72. The process of claim 71, wherein the nateglinide anhydrate is Form B.

73. The process of claim 71, wherein the nateglinide anhydrate is Form H.

10 74. The process of claim 71, wherein the nateglinide anhydrate is Form U.

75. The process of claim 71, wherein the nateglinide anhydrate is Form θ.

76. The process of claim 71, wherein stirring is carried out at a temperature of from about minus 15°C to about 10°C.

77. The process of claim 71, wherein the organic solvent is a mixture of a C₅ to a C₁₂ hydrocarbon and ethyl acetate.

15 78. The process of claim 77, wherein the hydrocarbon is heptane.

79. A process for preparing crystalline nateglinide of claim 65 comprising the step of stirring nateglinide Form U in a mixture of ethyl acetate and heptane for a sufficient time to obtain nateglinide of claim 65.

20 80. A process for preparing the crystalline nateglinide form of claim 65 comprising the steps of:

25 a) triturating a nateglinide in a solvent selected from the group consisting of dioxane, chloroform and tetrahydrofuran to obtain the crystalline form, with the proviso that the nateglinide triturated in chloroform is not Form H; and

b) recovering the crystalline form.

81. The process of claim 80, wherein the nateglinide triturated is Form U.

82. A process for preparing the crystalline form of claim 65 comprising the steps of:

25 a) preparing a solution of nateglinide in a mixture of ethyl acetate and heptane;

b) cooling the solution to precipitate a solid, thereby forming a mixture;

30 c) stirring the mixture for a sufficient time to obtain the crystalline form of claim 65;

and

d) filtering the mixture.

83. A process for preparing the crystalline form of claim 65 substantially free of residual solvent comprising the step of removing the residual solvent with a fluidized bed dryer.

84. The process of claim 83, wherein the crystalline form contains less than about 0.5% by weight of residual solvent after the removal process.

5 85. The crystalline form prepared by the process of claim 84.

86. A process for preparing the crystalline form of claim 65 substantially free of residual solvent comprising the step of removing the solvent under stirring at a temperature of at least about 40°C under vacuum.

87. A crystalline form of nateglinide (Form σ) characterized by data selected from the 10 group consisting of: an XRPD pattern with peaks at about 5.5, 6.1, 6.7, 14.3 ±0.2 degrees 2θ; DSC thermogram with an endotherm at about 127°C; and an FTIR spectrum with peaks at about 3303, 1705 and 1640 cm⁻¹.

88. The crystalline form of claim 87, wherein the crystalline form is characterized by an XRPD pattern with peaks at about 5.5, 6.1, 6.7, 14.3 ±0.2 degrees 2θ.

15 89. The crystalline form of claim 88, wherein the crystalline form has an XRPD pattern as substantially depicted in Figure 26.

90. A process for preparing the crystalline form of claim 87 comprising the step of stirring nateglinide Form B or Form U in an organic solvent for a sufficient time to obtain nateglinide Form σ.

20 91. The process of claim 90, wherein the form stirred is Form B.

92. The process of claim 90, wherein the organic solvent is a mixture of ethyl acetate and a C₅ to a C₁₂ aliphatic hydrocarbon.

93. The process of claim 92, wherein the hydrocarbon is heptane.

94. The process of claim 90, wherein the stirring is carried out at a temperature of about 25 minus 15°C to about 10°C.

95. A pharmaceutical formulation comprising nateglinide Form L, P, alpha, delta and sigma, and a pharmaceutically acceptable excipient.

96. A method for lowering blood sugar level in a mammal comprising administering the pharmaceutical formulation of claim 95 to the mammal.